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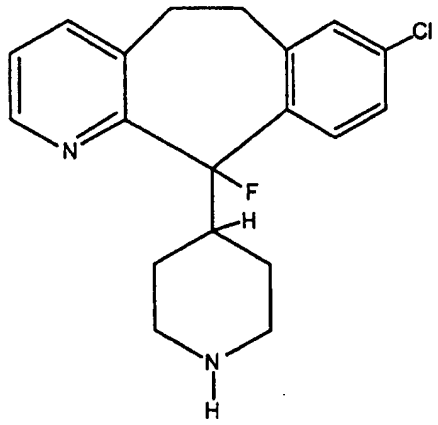

(III)

(57) Abstract

The present invention discloses uses of fluorinated descarboethoxyloratadine ("FDCL", Formula A) represented by formula (III), for preparation of medicaments for the treatment of allergic rhinitis and other allergies, including asthma, while avoiding the concomitant liability of adverse side–effects associated with other non–sedating antihistamines.

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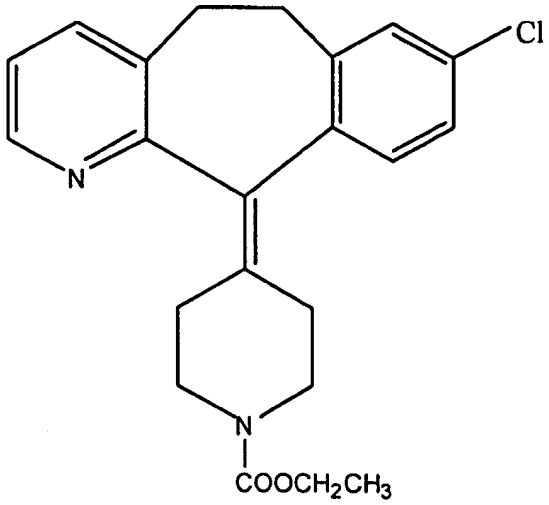
METHODS AND COMPOSITIONS FOR TREATING ALLERGIC AND RELATED DISORDERS USING FLUORINATED DESCARBOETHOXYLORATADINE

FIELD OF THE INVENTION

The present invention relates to methods of treatment involving the administration of a therapeutically effective amount of fluorinated descarboethoxyloratadine (desloratadine or "FDCL").

BACKGROUND OF THE INVENTION

Loratadine or 4-(8-chloro-5,6-dihydro-11H-benzo-[5,6]cyclohepta[1,2-b]pyridin-11-ylidene)-1-piperidinecarboxylic acid ethyl ester (Formula I) is an antagonist of the H_1 histamine receptor protein. The H_1 receptors are those that mediate the response antagonized by conventional antihistamines. H_1 receptors are present, for example, in the ileum, the skin, and the bronchial smooth muscle of man and other mammals.

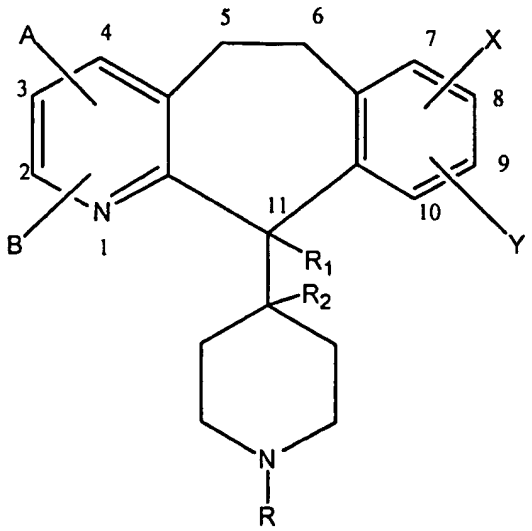


Formula I

Loratadine and pharmacologically active compositions comprising loratadine are disclosed in U.S. Patent 4,659,716 (issued April 21, 1987; assignee: Schering Corporation). That same US patent 4,659,716 further discloses a metabolite of loratadine,

descarboethoxyloratadine (desloratadine or DCL hereinafter). Other U.S. patents on DCL include U.S. 5,595,997 and 5,731,319 (both assigned to Sepracor, Incorporated).

U.S. Patent 4,863,931 (issued September 5, 1989; assignee: Schering Corporation) discloses antihistaminic fluorosubstituted benzocycloheptapyridines. Representative compounds in claim 1 of that patent have the structural formula (II):



Formula II

wherein A, B, X and Y are the same or different and independently represent H, halo, -CF_3, -OR^{10}, -$C(O)R^{10}$, -SR^{10}, -$N(R^{10})_2$, -$OC(O)R^{10}$, -CO_2R^{10}, -OCO_2R^{11}, alkyl, alkenyl, or alkynyl, which alkyl or alkenyl groups may be substituted with halo, -OR^{10}, or -CO_2R^{10};

R^{10} represents H, alkyl or aryl;

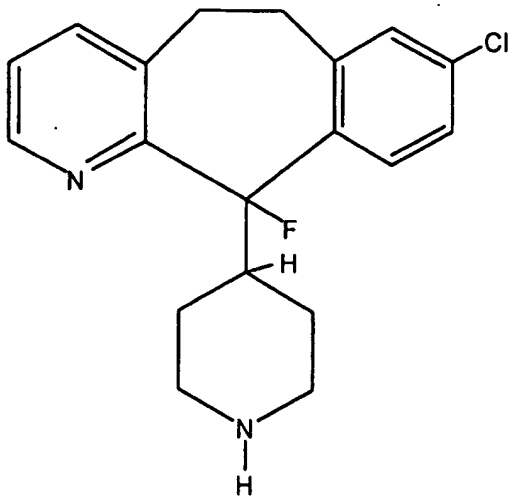
R^{11} represents alkyl or aryl;

R^1 and R^2 may be H and F respectively or F and H respectively; and

R is H, alkyl, or -CO_2R^{10} wherein R^{10} is as previously defined.

SUMMARY OF THE INVENTION

It has now been found that one member of the group of compounds disclosed within the disclosure and claim 1 of the above-referenced U.S. patent 4,863,931 wherein R= R^2= H, R^1 is F, A=B=Y=H, and X is at position C8 and is Cl (shown in Formula III) is particularly active and shows valuable pharmacological properties as an antihistaminic H_1 receptor antagonist.



Formula III

The present invention provides a method of treating allergic rhinitis and allergies, including asthma, in a human, comprising administering to such a human a composition, said composition comprising a therapeutically effective amount of a compound of Formula III (designated FDCL hereinafter) or a pharmaceutically acceptable salt thereof; and optionally a pharmaceutically acceptable carrier. The chemical name for FDCL is: 4-(8-chloro-5,6-dihydro-11-benzo-[5,6]-cyclohepta[1,2]-pyridin-11-fluoro)-piperidine. The present invention further provides methods to prepare such pharmaceutical compositions comprising FDCL and its salts.

The present invention still additionally discloses pharmaceutical compositions comprising FDCL (or a pharmaceutically acceptable salt thereof) and antagonists of neurokinin receptors as well as a method of treating allergic rhinitis, allergies, asthma and other respiratory diseases in a human, comprising administering to a human a composition, said composition comprising (i) a therapeutically effective amount of FDCL or a pharmaceutically acceptable salt thereof; and (ii) a neurokinin receptor antagonist.

This invention is also directed to a method of treating allergic rhinitis and allergies in a human while avoiding the concomitant liability of adverse side-effects associated with the administration of non-sedating antihistamines, comprising administering to a human a therapeutically effective amount of FDCL and a therapeutically effective amount of a decongestant.

Additionally, this invention provides a method of treating allergic rhinitis and allergies in a human while avoiding the concomitant liability of adverse side-effects

associated with the administration of non-sedating antihistamines, comprising administering to a human a therapeutically effective amount of FDCL and a therapeutically effective amount of a leukotriene receptor antagonist or a 5-lipoxygenase ("5-LO") inhibitor.

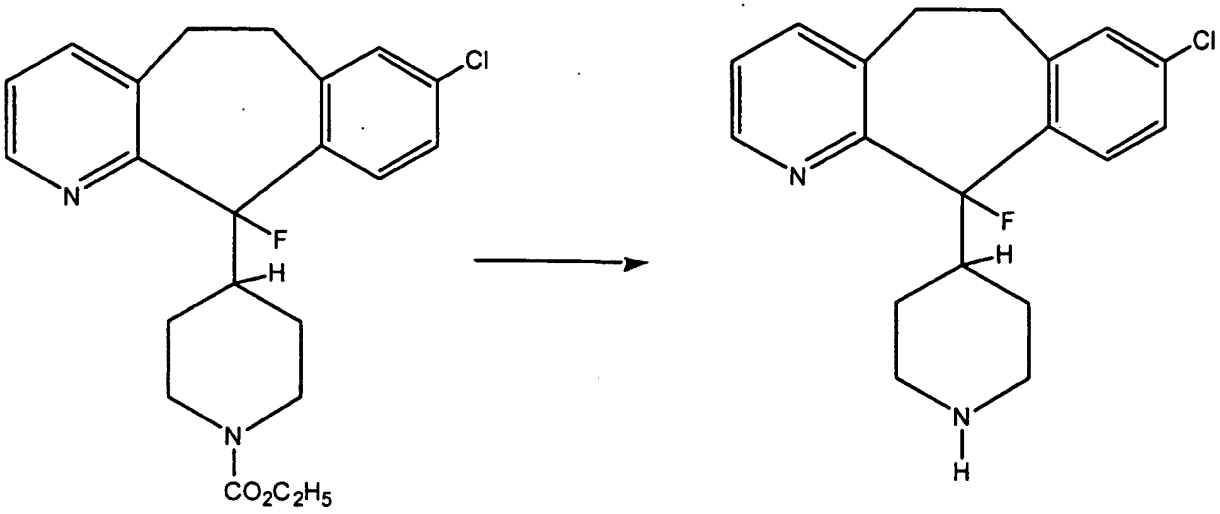
DETAILED DESCRIPTION OF THE INVENTION

The present invention encompasses a method of treating allergic rhinitis and allergies, including asthma, in a human while avoiding the concomitant liability of adverse side-effects associated with the administration of non-sedating antihistamines, comprising administering to a human a composition, said composition comprising (i) a therapeutically effective amount of FDCL or a pharmaceutically acceptable salt thereof, and (ii) a pharmaceutically acceptable carrier.

The composition may additionally contain therapeutically effective amounts of a decongestant, a leukotriene antagonist and/or a 5-lipoxygenase inhibitor.

FDCL may be prepared by any suitable means. One way of preparation is by the deesterification of a compound of Formula IV using a suitable acid such as, for example, 48% aqueous hydrofluoric acid, at suitable temperatures, e.g., 20-110°C, over suitable reaction times, e.g., 1-10 hours. Compound IV is described in the afore-mentioned U.S. patent 4,863,931. After the reaction, the product may be isolated by adding the reaction contents to a mixture of a suitable base and an organic solvent or solvents, and then isolating the product by suitable means such as, for example, solvent extraction, filtration and the like. The product may be purified by processes known in the art such as, for example, chromatography. Preparative HPLC using a suitable column and solvent yields the pure product which may be analyzed and characterized by methods known in the art.

The term "decongestant as used herein means any decongestant including, but not limited to phenylephrine, pseudoephedrine and phenylpropanolamine, and pharmaceutically acceptable salts thereof.



Formula IV Formula III

FDCL is basic and forms pharmaceutically acceptable salts with organic and inorganic acids. Examples of suitable acids for such salt formation include hydrochloric, sulfuric, phosphoric, acetic, citric, oxalic, malonic, salicylic, malic, fumaric, succinic, ascorbic, maleic, methanesulfonic and other mineral and carboxylic acids (both aliphatic and aromatic) well known to those skilled in the art. The salts may be prepared by contacting the free base form with sufficient amount of the desired acid to produce a salt in a conventional manner. The free base form may be regenerated by treating the salt with a suitable dilute aqueous base solution such as, for example, sodium hydroxide, potassium carbonate, ammonia and sodium bicarbonate. The free base form may differ from its corresponding salt form somewhat in certain physical properties such as, for example, solubility in polar solvents, but the salts are otherwise to be considered equivalent to the corresponding free base for purposes of this invention.

A further feature of this invention, therefore, is pharmaceutical compositions containing as the active ingredient a compound of Formula III (or salt, enantiomer, or tautomer thereof) together with a pharmaceutical carrier or excipient. The present invention thus also includes novel compositions for use in the inventive methods disclosed above.

The invention also includes pharmaceutical compositions containing FDCL with a H_3 antagonist and, use of such compositions for treating diseases associated with respiratory and allergic states.

The phrase "therapeutically effective amount" means that amount of FDCL which provides a therapeutical benefit in the treatment or management of allergic disorders such as urticaria, allergic rhinitis, symptomatic dermographism, dermatitis, allergic asthma, retinopathy or other small vessel disorders associated with diabetes mellitus, and the symptoms associated with allergic rhinitis such as cough, cold, cold-like, and/or flu symptoms including, but not limited to, sneezing, rhinorrhea, lacrimation, and dermal irritation.

The term "allergic asthma" is defined as a disorder characterized by increased responsiveness of the trachea and bronchi to various stimuli which results in symptoms which include wheezing, cough, and dyspnea.

The term "dermatitis" is that disorder caused by inflammation to the skin including endogenous and contact dermatitis such as, but not limited to: actinic dermatitis (or photodermatitis), atopic dermatitis, chemical dermatitis, cosmetic dermatitis, dermatitis aestivalis, and seborrheic dermatitis.

The term "leukotriene receptor antagonist" includes any agent or compound that inhibits, restrains, retards or otherwise interacts with the action or activity of leukotrienes, such as, but not limited to, 5-lipoxygenase inhibitors, 5-lipoxygenase activating protein ("FLAP") antagonists, and leuoktriene D_4 ("LTD_4") antagonists.

The term "5-lipoxygenase inhibitor" or "5-LO inhibitor" includes any agent, or compound that inhibits, restrains, retards or otherwise interacts with the enzymatic action of 5-lipoxygenase, such as, but not limited to, zileuton, docebenone, piripost, and the like. The term "5-lipoxygenase activating protein antagonist" or "FLAP antagonist" includes any agent or compound that inhibits, retrains, retards or otherwise interacts with the action or activity of 5-lipoxygenase activating protein, such as, but not limited to MK-591 and MK-886.

The term "leukotriene D_4 antagonist" or "LTD_4 antagonist" includes any agent or compound that inhibits, retrains, retards or otherwise interacts with the action or activity of leukotriene D_4, such as, for example, zafirlukast.

The magnitude of a prophylactic or therapeutic dose of FDCL in the acute or chronic management of an allergic disorder or condition will vary with the severity of the condition to be treated and the route of administration. The dose, and perhaps the dose frequency, will also vary according the age, body weight, and response of the individual

patient. Suitable total daily dose ranges can be readily determined by those skilled in the art. In general, the total daily dose range for FDCL, for the conditions described herein, is from about 0.1 mg to less than about 50 mg administered in single or divided doses orally, topically, transdermally, or locally by inhalation. For example, a preferred oral daily dose range should be from about 1 mg to about 10 mg. A more preferred oral dose is about 5 mg to about 10 mg. A preferred oral daily dose range of decongestant, such as pseudoephedrine, is from about 50 mg to about 300 mg, more preferably, about 150 mg to about 250 mg. In addition, suitable oral daily dosage ranges of leukotriene inhibitor can be readily determined by those skilled in the art.

It is further recommended that children, patients aged over 65 years, and those with impaired renal or hepatic function initially receive low doses, and that they then be titrated based on individual response(s) or blood level(s). It may be necessary to use dosages outside these ranges in some cases as will be apparent to those skilled in the art. Further, it is noted that the clinician or treating physician will know how and when to adjust, interrupt, or terminate therapy in conjunction with individual patient response.

The term "therapeutically effective amount of FDCL or a pharmaceutically acceptable salt thereof" is encompassed by the above-described dosage amounts. In addition, the terms "said composition comprising (i) a therapeutically effective amount of FDCL or a pharmaceutically acceptable salt thereof; and (ii) a therapeutically effective amount of a decongestant"; and "said composition comprising (i) a therapeutically effective amount of FDCL or a pharmaceutically effective amount of a leukotriene inhibitor" are also encompassed by the above-described dosage amounts and dose frequency schedule.

Any suitable route of administration may be employed for providing the patient with an effective dosage of FDCL according to the methods of the present invention. For example, oral, intraoral, rectal, parenteral, epicutaneous, transdermal, subcutaneous, intramuscular, intranasal, sublingual, intradural, intraocular, intrarespiratory, oral or nasal inhalation and like forms of administration may be employed. For the methods to treat dermatitis topical administration is preferred.

As stated earlier, the pharmaceutical compositions used in the methods of the present invention comprise FDCL as active ingredient, or a pharmaceutically acceptable

salt thereof, and may also contain a pharmaceutically acceptable carrier, and optionally, other therapeutic ingredients.

The compositions for use in the methods of the present invention may optionally include suitable excipients or carriers such as starches, sugars, microcrystalline cellulose, diluents, granulating agents, lubricants, binders, disintegrating agents, and the like.

Dosage forms include tablets, troches, dispersions, suspensions, solutions, capsules, patches, syrups, elixirs, gels, powders, magmas, lozenges, ointments, creams, pastes, plasters, lotions, discs, suppositories, nasal or oral sprays, aerosols and the like. Because of their ease of administration, tablets and capsules represent the most advantageous oral dosage unit form, in which case solid pharmaceutical carriers are employed. If desirable, tablets may be coated by standard aqueous or nonaqueous techniques.

In addition to the common dosage forms set out above, the compound for use in the methods of the present invention may also be administered by controlled release means and/or delivery devices. Such techniques are well known to those skilled in the art.

Pharmaceutical compositions for use in the methods of the present invention may be prepared by any of the methods of pharmacy, but all methods include the step of bringing into association the active ingredient with the carrier which constitutes one or more necessary ingredients. In general, the compositions are prepared by uniformly and intimately admixing the active ingredient with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product into the desired presentation.

For example, a tablet may be prepared by compression or molding, optionally, with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as powder or granules, optionally mixed with a binder, lubricant, inert diluent, surface active or dispersing agent. Molded tablets may be made by molding, in a suitable machine, a mixture of the powdered compound moistened with an inert liquid diluent. Desirable, each tablet contains from about 0.1 mg to less than about 10 mg of the active ingredient, and each cachet or capsule contains from about 0.1 mg to about less than 10 mg of the FDCL.

The invention is further defined by reference to the following examples describing in detail the preparation of the compound of Formula III and the compositions used in the

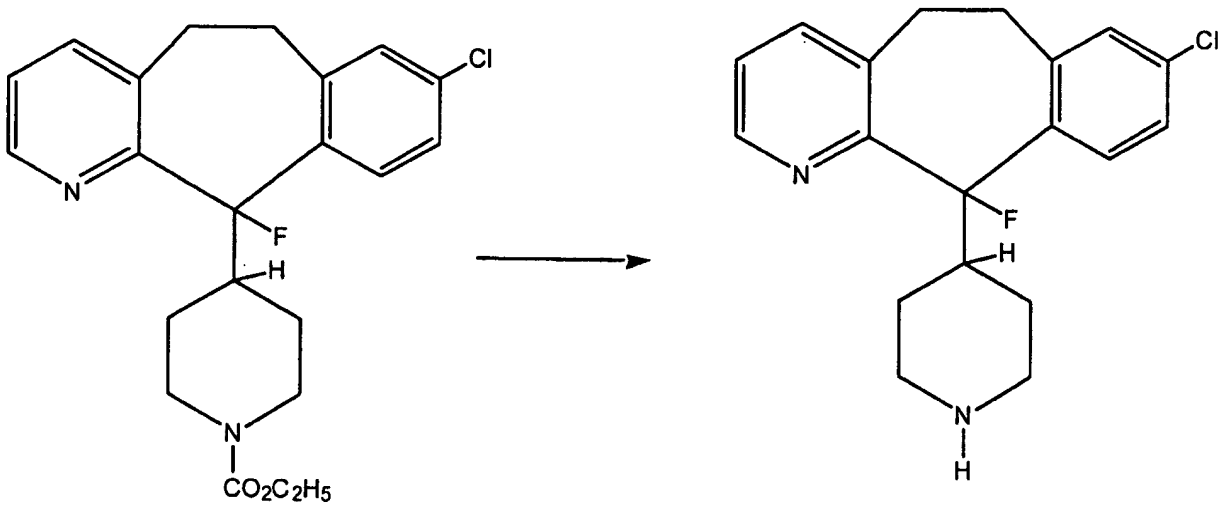
methods of the present invention, as well as their utility. It will be apparent to those skilled in the art that many modifications, both to materials and methods, may be practiced which are within the scope of this invention.

EXAMPLES

Example 1: Preparation of Fluorinated Desloratadine (FDCL):

(i) The compound of Formula IV was prepared starting from 2-cyano-3-methyl pyridine and 3-chlorobenzyl chloride using a multi-step synthetic process as described in the above-referenced U.S. Patent 4,863,931, which patent is incorporated herein by reference. One step in that process involved the use of HF, eventually yielding a compound of Formula IV.

(ii) The compound of Formula IV was converted to FDCL (Formula III) as follows:



Formula IV Formula III

Compound of Formula IV (4.75 g) was placed into a 200 ml polypropylene container, 50 ml of 48% HF is added and the container was heated in an oven at about 97 - 100° C for about 6-7 hours until the area percent amount of the starting material by analytical HPLC was less than 15%. To quench the reaction it was added dropwise to an ice cold mixture of 150 ml of acetonitrile, 300 ml of 29% NH_4OH, and 300 ml of tert-butyl methyl ether ("TBME") in a 1000 ml polypropylene container. The resulting mixture (pH>9.5) was transferred into a separatory funnel, organic layer containing the product was separated out and the aqueous layer was extracted again with 2 x 150 ml of TBME.

The combined TBME extracts were dried over Na_2SO_4 overnight, and evaporated to dryness yielding 4.8 g of crude product of Formula III (82% purity by area on HPLC).

This crude product was then purified by preparative HPLC to 98%+ area purity under the following conditions.

Column: YMC DIOL 200A, 15 μm, 5 x 20 cm

Mobile phase: TBME - 20 mM ammonium acetate in methanol 8:2

Flow: 240 ml/min

Detection: UV @ 270 nm

Upon recovery from the eluate, 2.36 g of a white crystalline substance (m.p. 295-297° C (decomp.) was obtained. NMR, MS, UV-spectra were consistent with the structure for Formula III.

Example 2: **Antihistaminic Activity of FDCL:** The binding affinity and the H_1 receptor antagonistic activity of FDCL were evaluated as follows:

A. **Binding Assay:**

I. Tissue preparation protocol for histamine H_1 receptor binding assay:

1. The tissue source was male Sprague-Dawley rat brain. These were purchased stripped and frozen (available from Rockland Corporation, Gilbertsville, Pennsylvania). The buffer used was ice-cold 50 mM Tris-HCL, pH 7.5. (The pH was determined at 25° C.)

2. The brains were spread out on plastic wrap on the benchtop and allowed to thaw for 10 - 15 min. After this, everything was kept ice-cold.

3. Two brains were put in each 50 ml round bottom centrifuge tube and 25 ml of buffer was added. Then they were broken up with a Polytron (from Brinkmann Instruments, Westbury, New York) equipped with a PT-10 tip at setting 6 for 30 sec. buffer was added. Then they were broken up with a Polytron at setting 6 for 30 sec.

4. The volume in the tube was brought up to 45 ml and mixed and the particulate material was centrifuged at 1000 *xg* (3000 rpm, SS-34 rotor) for 10 min to remove nuclei and unbroken cells.

5. Pellets were discarded and the supernatants were centrifuged 10 min at 50,000 *xg* (20,000 rpm, SS-34 rotor).

6. The high-speed pellets were resuspended in a volume of Tris buffer equal to the original (4 ml), the contents of all tubes were pooled, and a sample was taken for

BCA protein assay . The material was aliquotted, 45 ml per round-bottom tube, and the resuspension was recentrifuged. The yield of protein was approximately 20 mg/brain, so there was about 40 mg of protein per tube.

7. Pellets were frozen at -80° C.

II. H_1 Histamine receptor binding assay:

Materials: 96-well, deep-well, polypropylene plates, [^{3}H] pyrilamine, 20-30 Ci/mmol, from Dupont NEN Life Science Products, Boston, Massachusetts), chlorpheniramine maleate (from Schering-Plough Corporation, Kenilworth, New Jersey) as standard, stored as frozen 10^{-5}, 10^{-6}, 10^{-7}, 10^{-8}M solutions.

1. FDCL and comparative compounds for assay were independently solubilized at 1 mg/ml DMSO by vortexing, or if necessary by sonication. The first dilution, 100-fold, was made in 50 mM Tris-HCl, pH 7.5, at room temperature. The three or four subsequent ten-fold serial dilutions were made in 1% DMSO/50 mM Tris-HCl, pH 7.5. Drug solutions and assay plates were kept at room temperature during the course of the assay set up.

2. Test compounds were assayed at four or five concentrations: 1, 0.1, 0.01, 0.001, and 0.0001 μg/ml. Twenty μl of drug solution was pipeted into each of three wells. A chlorpheniramine maleate standard was assayed at 10^{-9} to 10^{-6} M, 20 μl of each of the appropriate solutions being pipeted into triplicate wells. Total and nonspecific (10^{-6} M chlorpheniramine maleate) binding were determined at least in quadruplicate. For total binding, 20μl of buffer was pipeted and for nonspecific 20 μl of 10^{-5} M chlorpheniramine maleate was pipeted into each well.

3. [^{3}H]Pyrilamine was diluted approximately 2000-fold with ice-cold mM Tris-HCl, pH 7.5 (to a working concentration of 20-25 nM), and put on ice.

4. A frozen tissue pellet was thawed in a 25°C water bath, resuspended in 50 mM Tris-HCl, pH 7.5, at 1.7-2 mg/ml by brief break-up on the Polytron, and put on ice.

5. Twenty μl of diluted [^{3}H]pyrilamine was added to each well.

6. One hundred fifty μl of tissue suspension was added to each well.

7. The top of the plate was covered and it was placed in a 25°C shaking water bath (about 60 oscillations/min) for 30 min..

8. Samples were filtered on a Tomtec Mach 2 harvester (available from Tomtec Corporation, Orange, Connecticut) through a GF/B filter mat (from Wallac, Inc., Gaithersburg, Maryland) presoaked in 0.3% polyethylenimine. Each sample was thrice washed with ice-cold 50 mM Tris-HCl, pH 7.5 dried 20 sec on the Tomtec, and dried 3-4 min in a microwave oven on a paper towel. The filter was impregnated with MELTILEX brand wax scintillant (from Wallac Corporation) and counted on a Betaplate scintillation counter (from Wallac Corporation).

9. Specific binding was determined as the difference between total and nonspecific binding. The percent inhibition in the presence of inhibitor or standard was determined using the formula:

[1-(sample binding-nonspecific binding)/specific binding]x100

For compounds that inhibit more than 50% at 1 μg/ml, an IC_{50} value was interpolated from proximate concentrations. The value was converted to a nM value using the compound formula weight and a K_i value was calculated using the equation of *Cheng and Prusoff* ($K_i=IC_{50}/(1+[L]/K_D)$, [*Y-C. Cheng and W.H. Prusoff,* "Relationship between the inhibitory constant (K_i) and the concentration of inhibitor which causes 50 per cent inhibition (IC_{50}) of an enzymatic reaction", *Biochem. Pharmacol.* 22 (1973) 3099-3108]. Lower value of K_i indicates greater binding affinity. The results obtained are presented in **Table 1**.

B. ***In vivo* Antihistaminic Activity Assay:** The oral antihistamine activity of FDCL and the comparative drugs was measured at 1 mg/kg and 3 mg/kg in guinea pigs (n= 6 per dose group; n= 11 in the vehicle control group). Animals were dosed 2 hours prior to i.v. challenge with histamine. The procedure was similar to that in U.S. patent 4,659,716 and ED_{50} values were similarly calculated. The results are reported in **Table 1**.

Table 1

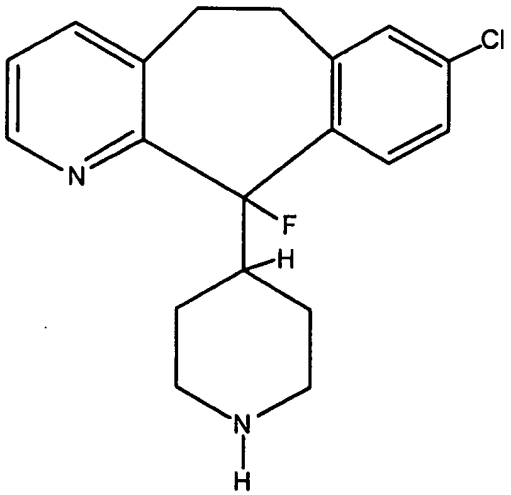
Compound	K_i (nM)	ED_{50} (mg/kg p.o.)
Loratadine	260	0.1
DCL	10	0.05
Fluoroloratadine	> 1,000	1 (for 85% inhibition) 0.3 (for 20% inhibition)
FDCL	46	0.25

As **Table 1** demonstrates, FDCL has excellent binding and antihistaminic properties.

CLAIMS

What is claimed is:

1. The use of fluorinated descarboethoxyloratadine ("FDCL") for the preparation of a medicament for treatment of allergic rhinitis and allergies in a human while avoiding the concomitant liability of adverse side-effects associated with the administration of non-sedating antihistamines,wherein the FDCL is represented by Formula A:



Formula A

2. The use as described in claim 1, wherein said treatment additionally comprises therapeutically effective amount of a decongestant.

3. The use as described in claim 1, wherein said treatment additionally comprises therapeutically effective amount of a neurokinin receptor antagonist.

4. The use as described in claim 1, wherein said treatment additionally comprises therapeutically effective amount of a leukotriene receptor antagonist.

5. The use as described in claim 1, wherein said treatment additionally comprises therapeutically effective amount of a 5-lipoxygenase inhibitor.

6. The use as described in claim 1, wherein the amount of FDCL administered is from about 0.1 mg to less than about 50 mg per day.

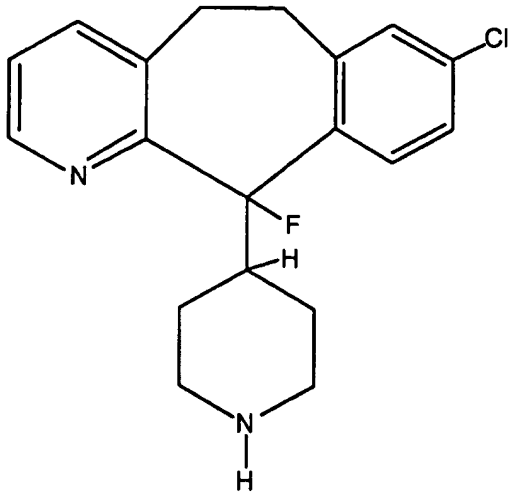
7. The use of claim 6 wherein the amount of FDCL administered is from about 1 mg to about 10 mg per day.

8. The use of claim 6 wherein the amount of FDCL administered is from about 5 mg to about 10 mg per day.

9. The use as described in claim 1, wherein said composition is administered orally.

10. The use as described in claim 1, wherein said composition is administered nasally.

11. A pharmaceutical composition for treating allergic rhinitis and allergies, said composition comprising as active ingredient therapeutically effective amount of fluorinated descarboethoxyloratadine ("FDCL", Formula A) or a pharmaceutically acceptable salt thereof:

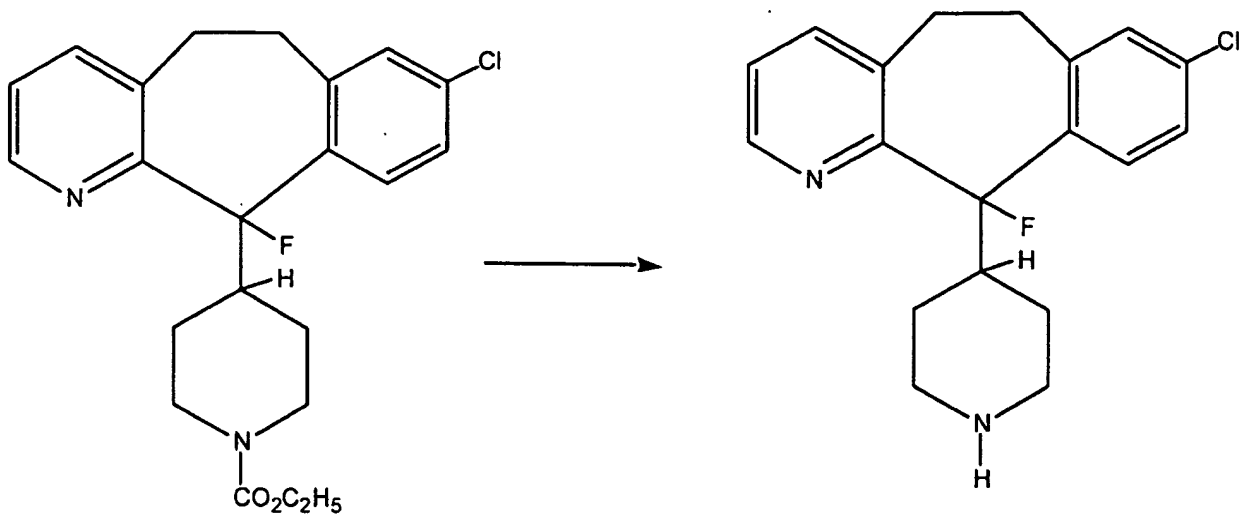


Formula A

12. The composition of claim 11, additionally comprising a pharmaceutically acceptable carrier.

13. The composition of claim 11, additionally comprising therapeutically effective amount of a decongestant.

14. A process of preparing fluorinated descarboethoxyloratadine ("FDCL", Formula A), said process comprising: (a) reacting a compound of Formula B with an acid at about 20-110°C for a period of about 1-10 hours to prepare a first mixture;



Formula B Formula A

(b) intimately mixing said first mixture of step (a) with a second mixture comprising a base and an organic solvent;

(c) isolating FDCL from step (b); and

(d) purifying the FDCL by chromatographic means.

15. The process of claim 14, wherein said acid is 48% aqueous hydrofluoric acid.

16. The process of claim 14, wherein said base is ammonium hydroxide.

17. The process of claim 14, wherein said organic solvent is acetonitrile.

INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/US 00/08080

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/445 A61P11/02 A61P11/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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Y	US 5 595 997 A (ABERG A K GUNNAR ET AL) 21 January 1997 (1997-01-21) cited in the application the whole document	1-13
Y	WO 97 28797 A (MERCK & CO INC ;DAHLEN SVEN ERIK (SE); SCOLNICK EDWARD M (US)) 14 August 1997 (1997-08-14) the whole document	1-13

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

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"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
5 September 2000	12/09/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Veronese, A

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INTERNATIONAL SEARCH REPORT

Information on patent family members

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